page 27 lines 5-10 and page 28 lines 4-12 and examples (cDNA). A copy of all of the pending claims as they are believed to have been amended is attached to this Amendment as an appendix.

The present invention is directed to the alteration of hormone levels via the inhibition of SR-BI receptor function or expression or selectively increasing the expression of SR-BI by a compound such that the resulting, direct and selective, uptake of cholesterol or cholesteryl ester by steriodogenic tissues is altered.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1-16 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The key to the present invention is the evolutionary conservation between the SR-BI molecules in mice and humans. This conservation allows for familiar and routine experimentation to be conducted by one of skill in the art as well as for careful extrapolation of results obtained from such experimentation. Routine assays and experiments such as Northern blot analysis, ligand binding, uptake and degradation assays, competition binding studies, and gene expression assays as described in the specification are all common procedures in the art. Common and routine assays, combined with the evolutionary conservation of the SR-BI receptor between species, eliminates undue experimentation and alleviates many of the problems that may arise when trying to elucidate information from proteins that have no known functional counterparts in other species.

The examiner states that "function cannot be predicted based solely on structural similarity to a protein found in the sequence databases". The examiner must take into account that the applicant has more data at his disposal than that of sequences of potential ligands to SR-BI. The cDNA encoding SR-BI has been cloned. The nucleotide sequence encodes a protein of 509 amino acids which is 30% identical to three of the previously described CD36 proteins. Ligands that bind to SR-BI have been described and characterized, genetically and biochemically, in detail (AcLDL, LDL, estrogen, HDL, anti-SR-BI antibodies). The full-length DNA required for normal transcription of SR-BI is known and disclosed in the present specification. This sequence is critical to the modification and design of hybridizing or "complementary" compounds. *The targeted sequence encoding SR-BI defines the complementary nature of the compounds* to be designed. Details such as binding the minor or major groove of the nucleic acid, orientation of hydrogen bonds and how many hydrogen bonds, can readily be predicted simply by looking at the targeted sequence and/or by inserting the sequence into any number of commercially available programs. Determining whether or not a known sequence is bound or can be bound by a protein or anti-sense oligonucleotide can be accomplished by methods that are well known in the art.

The examiner has provided many references which address protein annotation and computer analysis of genome sequences. Many of the references are concerned with addressing the problems encountered while trying to assign function to *random* genomic sequences. Applicant respectfully submits that annotating sequences as genes with particular functions based solely on their identified sequence in a "sea" of random ATGC's that make up a particular

genome is completely different from modeling based on structural, biochemical, and genetic data derived from the targeted receptor and already known interacting compounds of interest. Additionally, in many cases, it is not necessary to compare the full length structure of two proteins. One is able to search and define domains within a given protein structure, even if "information is taken from the one-line description of the best data-base match". Misleading data are typically the result of not methodically "breaking up" or separating the larger structure into domains and conducting smaller domain searches. When analyzing the sequence of receptors for potential leads as to how to design binding inhibitors or activators, one typically focuses in on the residues that make up the binding pocket or cleft of the protein. Obviously this is crucial to the functionality of the receptor. Given the data and evidence of record, the applicant can approach the design of the claimed compounds from two very different angles significantly reducing the number of questions that may arise when trying to determine specific details of protein function. The applicant can design compounds based on models of already existing ligands as well as models of SR-BI and CD36 receptors. Note that this experimentation would not be undue given the assays and computer modeling programs available to the applicant.

The applicant respectfully submits that base claim 1 as amended and the claims dependent thereon overcome all rejections under 35 U.S.C. § 112.

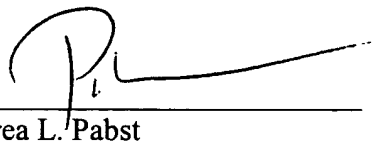
Rejection Under 35 U.S.C. § 102

Claims 1-7, 15 and 16 were rejected under 35 U.S.C. § 102(a) as being anticipated by *Current Opinion in Lipidology* (1997), 8:181-188 by Rigotti *et al* ("Rigotti"). The applicant respectfully traverses this rejection to the extent that it is applied to the claims as amended.

The applicant has stated that estrogen is associated with a number of side effects and that treatment is more preferably achieved through other agents. Example 3, in the specification provides evidence that SR-BI expression is dramatically down-regulated under conditions of tremendous up-regulation of the LDL-receptor when rats are treated with estrogen. Estrogen mediates many of it's effects *through* this up-regulation of LDL-receptor expression. Steroids, such as estrogen, typically bind to and activate target receptors in the nucleus. Upon activation, the receptor binds to the "hormone responsive elements" of the target gene and activates transcription/expression of the gene. Therefore, the limiting term "selectively" of base claim 1 defines the compound as one that selectively increases SR-BI expression and results in the *direct selective* alteration of cholesterol or cholesteryl ester transfer. Compounds such as estrogen mediate their effects through activities such as the up-regulation of LDL-receptors by targeting their expression as well as by binding to other estrogen receptors. Base claim 1 of the present invention does not encompass such activities. As stated in the applicant's response to the Office Action mailed on January 3, 2001, "none of estrogen, human chorionic gonadotrophin, or dexamethasone selectively increase SR-BI but have a wide range of other activities". Additionally, because of these other activities, none of these hormones or the compound result in the direct, selective alteration of cholesterol or cholesteryl ester uptake. The applicant respectfully submits that Rigotti does not disclose a compound that *selectively* increases SR-BI expression to *directly* and *selectively* alter the transfer of cholesterol or cholesteryl ester to steroidogenic tissues.

Allowance of claims 1-16 is respectfully solicited.

Respectfully submitted,



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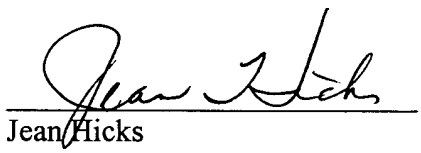

Jean Hicks

Date: July 11, 2001

Marked Up Version of Amended Claims
Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

1. (Three times amended) A method for modifying steroid production in a mammal in need of treatment by alteration of reproductive hormone levels comprising administering a compound directly inhibiting SR-BI function or expression or a compound selectively increasing expression of SR-BI thereby directly resulting in the selective [altering] alteration of cholesterol or cholesteryl ester from high density lipoprotein or other lipoproteins by specifically altering expression of or binding to cholesterol or cholesteryl ester of SR-BI to steroidogenic tissues producing reproductive hormones, wherein the compound is selected from the group consisting of SR-BI cDNA, SR-BI anti-sense nucleic acids, SR-BI antibodies, and SR-BI receptor binding small molecules or proteins.

2. The method of claim 1 wherein the compound alters SR-BI expression in the tissue.

3. The method of claim 1 wherein the compound alters binding of SR-BI to high density lipoprotein including cholesteryl ester or other lipoproteins.

4. The method of claim 2 wherein the compound decreases SR-BI expression in the tissue.

5. The method of claim 2 wherein the compound increases SR-BI expression in the tissue.

6. The method of claim 3 wherein the compound decreases SR-BI binding to lipoprotein or transfer of cholesteryl ester in the tissue.

7. The method of claim 3 wherein the compound increases SR-BI binding to lipoprotein or transfer of cholesteryl ester in the tissue.

8. The method of claim 1 wherein the mammal is a female and the compound is administered in an amount effective to prevent normal reproductive function.

9. The method of claim 1 wherein the mammal has a disorder characterized by overproduction of steroids.

10. The method of claim 1 wherein the mammal has a disorder characterized by underproduction of steroids.

11. The method of claim 10 wherein the disorder is menopause.

12. The method of claim 1 wherein the mammal has a disorder which can be treated by decreasing production of steroids.

13. The method of claim 12 wherein the disorder is breast or prostate cancer.

14. The method of claim 12 wherein the disorder is endometriosis or fibroid tumors.

15. The method of claim 1 wherein the compound differentially alters the activity of, or expression of, SR-BI in different tissues.

16. The method of claim 11 wherein the compound increases SR-BI expression in reproductive tissues and decreases or does not increase SR-BI expression in liver.